PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2007/058440	15.08.2007	16.08.2006

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/185 A61K31/192 A61K31/222 A61K31/216 A61K31/255 A61P35/00 A61K45/06

Applicant
ACTION MEDICINES, S.L.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

European Patent Office - P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tx: 31 651 epo nl
Fax: +31 70 340 - 3016

Date of completion of this opinion
see form PCT/ISA/210

Authorized Officer
Strack, Eberhard

Telephone No. +31 70 340-4760

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2007/058440

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 1-17 (partially)

because:

☒ the said international application, or the said claims Nos. 15-17 with regard to patentability relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for the whole application or for said claims Nos. 1-17 (partially)

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-8, 11-14
	No:	Claims	1, 2, 9, 10, 15-17
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	3-8, 11-14
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	-

2. Citations and explanations

see separate sheet

Re Item III

III.1 Claims 15-17 relate to a subject matter considered by this authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT. Although these claims are directed to a method of treatment of the human/animal body, the search has been carried out based on the alleged effects of the composition. Likewise, an opinion as to novelty, inventive step and industrial applicability will be given taking these alleged effects into account.

III.2 Present claims 1-17 relate to an extremely large number of compounds defined (inter alia) by reference to the expression

"isomer or prodrug".

Support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.

Independent of the above reasoning, resulting from the use of this expression, the claims contain so many options and variables that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Consequently, the search for claims 1-17 has been restricted to those parts of the application which do appear to be clear (and concise), supported and disclosed, namely the use of compounds of Formula I (including salts and solvates thereof) in relation to the diseases claimed with due regard to the general idea underlying the present invention.

III.3 No opinion will be given in respect of subject-matter which is not covered by the search report.

Re Item V

An opinion will be given only in respect of subject-matter which is covered by the search report (Rule 66.1 (e) PCT), i.e. the subject-matter limited as outlined under the previous section(s).

Claims 15-17 relate to a subject matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT. The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for use in a first or further medical treatment.

V.1 The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: CUEVAS PEDRO ET AL: "Treatment of basal cell carcinoma with dobesilate." JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY SEP 2005, vol. 53, no. 3, September 2005 (2005-09), pages 526-527, XP005031150 ISSN: 1097-6787

D2: WO 96/25159 A (US HEALTH [US]) 22 August 1996 (1996-08-22)

D3: STANWELL C ET AL: "THE ERBSTATIN ANALOGUE METHYL 2,5-DIHYDROXYCINNAMATE CROSS-LINKS PROTEINS AND IS CYTOTOXIC TO NORMAL AND NEOPLASTIC EPITHELIAL CELLSBY A MECHANISM INDEPENDENT OF TYROSINE KINASE INHIBITION" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, US, vol. 55, no. 21, 1 November 1995 (1995-11-01), pages 4950-4956, XP000569613 ISSN: 0008-5472

D4: YAMADA K ET AL: "Inhibitory effect of diacetyl gentisic acid on melanogenesis" NIHON KOSHOHIN KAGAKKAISHI - JOURNAL OF JAPANESE COSMETIC SCIENCE SOCIETY, NIHON KOSHOHIN KAGAKKAI,TOKYO, JP, vol. 22, no. 3, 1998, pages 169-174, XP008088000 ISSN: 0287-1238

Unless otherwise mentioned, the passages cited in the international search report are considered to represent the pertinent passages of said documents.

V.3 Article 33(2) PCT

V.3.1 The subject-matter of independent claims 1 and 15 and dependent claims 2, 9, 10 and 16-17 (in as far as the objections under Item III can be overcome) cannot be regarded novel in the sense of Article 33(2) PCT for the following reasons:

D2 discloses the treatment of various skin cancers and various pre-malignant skin lesions (and thus the prophylaxis of skin cancer as presently claimed) with 2-phenylethyl 2,5-dihydroxycinnamate.

The subject-matter of claims 1, 2, 9, 10 and 15-17 can therefore not be regarded novel over said document.

Similar, D3 discloses methyl 2,5-dihydroxycinnamate for the treatment of neoplastic lesions of the skin, e.g. squamous carcinoma cell lines. The advantages of topical administration of said compounds are particularly stressed.

The subject-matter of claims 1, 2, 9, 10 and 15-17 can therefore not be regarded novel over said document.

V.4 Article 33(3) PCT

V.4.1 In as far as the objections of lack of novelty raised above could be overcome, claims 1, 2, 9, 10 and 15-17 would still lack an inventive step over D2 and D3, as the subject-matter of the present claims in as far as it could be novel appears to be obvious in the sense of Article 33(3) PCT over said documents.

V.4.2 The subject-matter of dependent claims 11 (oral and further modes of administration), 12 (unspecified combination treatments) and 13-14 (combination treatments for which no specific advantage over the prior art is given) can also not be regarded inventive in the sense of Article 33(3) PCT over D2 and D3 (in combination with common knowledge at the priority date). Said dependent claims do not contain any technical feature which could be regarded as inventive per se.

Furthermore, with regard to claims 3-8, in the absence of suitable experimental data, the use of said compounds appears to represent an obvious alternative vis-à-vis D2 and D3: the skilled person would consider the use of said compounds for anti-skin cancer treatment as the modifications over D2 and D3 are minor and therefore obvious modifications within the ambit of the skilled person, in particular with regard to the preferred compound 2,5-dihydroxycinnamic acid.

V.4.3 In addition, the subject-matter of the application can also not be regarded inventive over D1, which discloses dobesilate use for the treatment of basal cell carcinoma.

The problem to be solved appears to be the provision of an alternative treatment of skin cancer, such as basal cell carcinoma.

The solution, i.e. the use of the compounds of Formula I is obvious: the skilled person would consider the use of said compounds for skin cancer treatment as the structural modification vis-à-vis D1 (the compound of D1, dobesilate, excluded by the proviso of claims 1 and 15) is a minor and therefore obvious modification within the ambit of the skilled person.

Similarly, the subject-matter of the application can also not be regarded inventive over D4 which discloses the inhibitory effect of diacetyl gentisic acid (a compound differing from the present application in that R1 is Z instead of Y) on melanogenesis.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPER (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

XS CPRTENFRDE